REMARKS

Claims 1, 9, 10, 12, 14, and 15 have been amended. Support for the amendments can be found in Claims 1, 9, 10, 12, 14, and 15 as originally filed. No new matter has been introduced by these amendments. The following addresses the substance of the Office Action.

Finality of the Office Action

The Examiner has indicated that applicant's amendment necessitated the new grounds of rejection, and therefore this Office Action was made final. Applicant respectfully disagrees. According to MPEP 706.07:

> "To bring the prosecution to as speedy conclusion as possible and at the same time to deal justly by both the applicant and the public, the invention as disclosed and claimed should be thoroughly searched in the first action and the references fully applied; and in reply to this action the applicant should amend with a view to avoiding all the grounds of rejection and objection. " (emphasis ours)

Here, the first Office Action cited no prior art. Claim amendments introduced by the previously filed response added specific phenotypic characteristics of Schwann or schwannoma cells in response to indefiniteness rejection. These added phenotypic characteristics merely clarified the invention, but did not change the underlying invention. Indeed, the teachings of the references now cited by the Examiner do not address these added phenotypic characteristics. Instead, the references are directed to the more fundamental aspects of the invention. Specifically, the Peden et al. reference now cited by the Examiner describes production of rat Schwann cell lines by introducing an immortalizing gene into the primary culture of rat Schwann cells. Roque et al., Schlegal et al. and Katakura et al. all teach that HPV16 E6 and E7 proteins had been used in the art to immortalize mammalian cell lines. The limitations of immortalizing a Schwann cell line by introducing an immortalizing gene into the cells of primary culture of Schwann cells were in the claims at the time of the first Office Action. Therefore, the Examiner should have presented these references in the first Office Action to give the Applicant a chance to address these references then. Therefore, the finality of this Office action is clearly improper and should be withdrawn.

Claim Objections

The Examiner has objected to Claims 1, 9, 10, 12 and 14. Specifically, claims 1, 9 and 12 do not spell out the complete name of the NF2 gene followed by the abbreviation in parentheses; Claim 10 has a typographical error: the term "adenovirus EA" should have been spelled as

"adenovirus E1A"; the noun "gene" in claims 12 and 14 should have been in a plural form. Claims 1, 9, 10, 12 and 14 have been amended accordingly.

Specification

The Examiner has objected to the Specification for a typographical error on page 8, line 10: the term "adenovirus EA" should have been spelled as "adenovirus E1A". The Specification has been amended accordingly.

Enablement

The Examiner has rejected Claims 1-21 under 35 USC §112, first paragraph as being non-enabled. Specifically, the Examiner stated that the Specification does not provide enablement for introducing an NF2 mutation into human Schwann cell lines or methods for selecting immortalized cells that have a mutant NF2 gene. Applicant has amended Claim 1 to the method of producing an immortalized human schwannoma cell line from a primary culture of schwannoma cells having a mutation in NF2 gene, the immortalized human schwannoma cell line retaining the mutant NF2 gene. Claims 1-21 have been limited to the immortalized human schwannoma cell line. The Examiner indicated that these claims are enabled by the specification as filed. Therefore, the rejection of currently amended claims 1-21 under 35 USC §112, first paragraph should be withdrawn.

Definiteness

The Examiner has rejected Claim 14 under 35 USC §112, second paragraph, as being indefinite for reciting the phrase "substantially pure". Claim 14 has been amended per the Examiner's suggestion to now recite "An isolated". Claims 9 and 12 have been amended similarly to Claim 14. Therefore, Claims 9, 12 and 14 are all definite, and the rejection of Claim 14 under 35 USC §112, second paragraph should be withdrawn.

Non-obviousness

The Examiner has rejected Claims 1, 2 and 6 under 35 USC §103(a) as being unpatentable over Peden et al. (*Ann. N.Y. Acad. Sci.* **605**:286-293, 1990). Specifically, the Examiner stated that it would have been obvious at the time the invention was made to a person with ordinary skill in the art to substitute primary culture of Schwann cells from a rodent (rat) with Schwann cells from a human to produce an immortalized cell culture by introducing an exogenous immortalizing gene into the primary cell culture. Applicants respectfully disagree.

First, Claims 1-21 have now been limited to an immortalized human Schwannoma cell line having a mutant NF2 gene. Peden does not teach or suggest using schwannoma cells having a pre-existing NF2 mutation. As stated in the Specification on page 2, lines 15-20:

> "To date, no single cell line has been developed from NF2 tumor cells, and most studies were conducted either in yeast, mouse schwannoma cells or other non-Schwann human cells. There are three main reasons for this limited progress. First, human Schwann cells are difficult to obtain. Second, because of the lack of knowledge of Schwann cell growth factors, once the Schwann cells are obtained, they do not proliferate in culture. Third, there is the contamination of human fibroblast."

The further, on page 2, lines 25-33:

> "Human Schwann or schwannoma cells are essential for the study of NF2 tumorigenesis. In the past, researchers have had to rely on primary cultures of these cells for NF2 research. Such cultures have been of limited value, however, for the following reasons: 1) human Schwann cells are difficult to obtain, 2) very small numbers of cells can be obtained and cultured, 3) the cultures can be maintained for short periods of time and die quickly, and 4) fibroblasts often overgrow the culture.
>
> The establishment of an NF2 cell line is therefore of significant value as it obviates the need for using primary cultures and enables scientists to perform studies that would not have been possible using primary cultures."

The present inventors were the first ones to successfully obtain such an immortalized NF2 cell line, by obtaining a primary culture of human vestibular schwannoma cells having a pre-existing mutation in NF2 gene and transfecting these cells with HPV-16 E6-E7 genes thereby obtaining an immortalized culture.

Second, there has been a long-felt and unmet need for a human schwannoma cell line, despite the 1990 teaching of Peden et al. As stated in the Inventor's Declaration submitted herewith, prior to the presently claimed invention, everyone had been working on mouse Schwann cell lines or spontaneously immortalized cell lines (mouse), or human xenografts implanted into mice. Thus, as discussed by Dr. Hung in his declaration, even though the Peden article taught methodology for immortalizing normal rat Schwann cells, no one was successful in immortalizing a human Schwann cell line; and indeed, no one was even motivated to try to immortalize human tumorigenic schwannoma cells.

As soon as Applicants had reported their human schwannoma cell line, it was immediately requested by 18 groups for their research, and one of these groups (Massachusetts General Hospital, already published the results of their experiments with the claimed Schwannoma cell line (see Prabhakar et al. 2007 *Cancer Gene Therapy* 14:460-467, submitted herewith for the Examiner's convenience). Therefore, there was a long-felt and unmet need that the creation of the claimed invention was able to meet, followed by its commercial success in the scientific community.

Furthermore, as the Examiner acknowledged on page 5 of the Office Action: "The inventive concept in the instant application is the isolation of a human Schwannoma cell line from patients suffering from neurofibromatosis, wherein the tumorigenic Schwannoma cells comprise a pre-existing mutation in the endogenous NF2 gene."

For the foregoing reasons, currently amended claims 1, 2 and 6 are non-obvious over the Peden reference and Applicants respectfully request that their rejection under 35 USC §103(a) be withdrawn.

The Examiner has rejected Claims 3-5, 7 and 8 under 35 USC §103(a) as being unpatentable over Peden et al. (*Ann. N.Y. Acad. Sci.* **605**:286-293, 1990) as applied to Claim 1 above, and further in view of Roque et al. (*Exp. Eye Res.* 64:519-527, 1997), Schlegal (USP 5,376,542) and Katakura et al. (1998, of record). Specifically, the Examiner stated that it would have been obvious to a person skilled in the art at the time the invention was made to substitute the immortalizing gene of Peden et al. with the HPV-16 E6 and E7 proteins or E1A protein as taught by Rogue et al., Schlegal et al. and Katakura et al. However, as asserted above, Claim 1 is not obvious over Peden et al. The additional cited references do not cure the deficiencies of the Peden reference. Therefore, Claims 3-5, 7 and 8 are non-obvious of the combination of the cited art, and their rejection under 35 USC §103(a) should be withdrawn.

The Examiner has rejected Claim 9 under 35 USC §103(a) as being unpatentable over Peden et al. (*Ann. N.Y. Acad. Sci.* **605**:286-293, 1990) and Rosenbaum et al. (*Neurobiology of Disease* 5:55-64, 1998). Specifically, the Examiner stated that it would have been obvious to a person skilled in the art at the time the invention was made to substitute the rat Schwann cells immortalized by the method taught by Peden et al. with the human Schwannoma cells taught by Rosenbaum et al. with a reasonable expectation of success. However, as discussed above, no one

got that success or was motivated to try, until the present inventors created the claimed immortalized human schwannoma cell line, which was immediately requested by eighteen research groups both in the United States and abroad— which attests for a long-felt need in the scientific community for such a cell line and for its commercial success. Therefore, the combination of Peden and Rosenbaum does not make claim 9 obvious, and its rejection under 35 USC §103(a) should be withdrawn.

The Examiner has rejected Claim 10 under 35 USC §103(a) as being unpatentable over Peden et al. (*Ann. N.Y. Acad. Sci.* **605**:286-293, 1990) and Rosenbaum et al. *(Neurobiology of Disease* 5:55-64, 1998) as applied to Claim 9, and further in view of Katakura et al. (1998, of record). Specifically, the Examiner stated that it would have been obvious to a person skilled in the art at the time the invention was made to substitute the immortalizing gene of Peden et al. with the HPV-16 E6 and E7 proteins or E1A protein as taught by Katakura et al. As asserted above, Claim 9 is non-obvious over Peden and Rosenbaum. Katakura fails to cure the deficiencies of the two primary references. Therefore, Claim 10 is non-obvious of the cited combination, and its rejection under 35 USC §103(a) should be withdrawn.

The Examiner has rejected Claim 11 under 35 USC §103(a) as being unpatentable over Peden et al. (*Ann. N.Y. Acad. Sci.* **605**:286-293, 1990), Rosenbaum et al. (*Neurobiology of Disease* 5:55-64, 1998) and Katakura et al. (1998, of record) as applied to Claims 9 and 10, and further in view of Schlegal et al. (USP 5,376,543). Specifically, the Examiner stated that it would have been obvious to a person skilled in the art at the time the invention was made to substitute the immortalizing gene of Peden et al. or Katakura et al. with the HPV-31, 33 or 35 E6 and E7 proteins as taught by Schlegal et al. As asserted above, Claims 9 and 10 are non-obvious over Peden, Rosenbaum and Katakura. Schlegal et al. fail to cure the deficiencies of the three primary references. Therefore, Claim 11 is non-obvious of the cited combination, and its rejection under 35 USC §103(a) should be withdrawn.

The Examiner has rejected Claims 12 and 13 under 35 USC §103(a) as being unpatentable over Peden et al. (*Ann. N.Y. Acad. Sci.* **605**:286-293, 1990), Rosenbaum et al. (*Neurobiology of Disease* 5:55-64, 1998), Roque et al. (*Exp. Eye Res.* 64:519-527, 1997), Schlegel et al. (USP 5,376,543) and Katakura et al. (1998, of record) as evidenced by Li et al. (*Cancer Biotherapy and Radiopharm.* 18:829-840, 2003). Specifically, the Examiner stated that

it would have been obvious to a person skilled in the art at the time the invention was made to substitute the rat Schwann cells immortalized by the method taught by Peden et al. with the human Schwannoma cells taught by Rosenbaum et al. and the immortalizing gene of Peden et al. with either the HPV-16 E6 and E7 proteins or adenovirus E1A protein as taught by Katakura et al., Schlegal et al. and Rogue et al. However, as discussed above with regards to non-obviousness of Claims 1 and 2, the present inventors were the first ones to successfully obtain an immortalized human NF2 cell line, by obtaining a primary culture of human vestibular schwannoma cells having a pre-existing mutation in NF2 gene and transfecting these cells with HPV-16 E6-E7 genes thereby obtaining an immortalized culture. As stated in the Inventor's Declaration submitted herewith, prior to the presently claimed invention, everyone had been working on mouse Schwann cell lines or spontaneously immortalized cell lines (mouse), or human xenografts implanted into mice. As soon as the claimed cell line became available, it was requested by 18 groups for their research, and one of these groups (Massachusetts General Hospital) already published the results of their experiments with the claimed Schwannoma cell line (see Prabhakar et al. 2007 *Cancer Gene Therapy* 14:460-467, submitted herewith for the Examiner's convenience). Therefore, there was a long-felt need that the creation of the claimed invention was able to provide solution to, followed by its commercial success in the scientific community.

Furthermore, as the Examiner accnowledged on page 5 of the Office Action: "The inventive concept in the instant application is the isolation of a human Schwannoma cell line from patients suffering from neurofibromatosis, wherein the tumorigenic Schwannoma cells comprise a pre-existing mutation in the endogenous NF2 gene."

Therefore, Claims 12 and 13 are non-obvious over the combination of the cited references, and their rejection under 35 USC §103(a) should be withdrawn.

The Examiner has rejected Claims 15-21 under 35 USC §103(a) as being unpatentable over Peden et al. (*Ann. N.Y. Acad. Sci.* **605**:286-293, 1990), and Rosenbaum et al. (*Neurobiology of Disease* 5:55-64, 1998), as applied to Claim 9, and further in view of Einheber et al. (*JBC* 129:443-458, 1995), Bonetti et al. (*J. Neuropathol. Exp. Neurol.* 59:74-84, 2000) and Steele et al. (*Carcinogenesis* 21:63-67, 2000). Specifically, the Examiner stated that it would have been obvious to a person skilled in the art at the time the invention was made to substitute the cell

types as taught by Einheber et al., Bonetti et al. and Steele et al. with the immortalized human Schwann or Schwannoma cells. However, the non-obviousness of currently amended claims 9 and 12 over Peden et al. and Rosenbaum et al. has been asserted above. Claims 15-21 depend from these non-obvious claims. The secondary references of Einheber et al., Bonetti et al., and Steele et al. fail to cure the deficiencies of the primary references. Therefore, Claims 15-21 are non-obvious over the cited combination of references, and their rejection under 35 USC §103(a) should be withdrawn.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: October 4, 2007

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